Remarks

Applicants had elected Group I, claims 1-13 and 17-23 in response to a restriction, and in response to a species election had elected stroke as the of neurological disorder to initially be examined. In the Office Action: claims 1-7, 12-13 and 17-23 were rejected as lacking enablement; claims 1-7, 12-13 and 17-23 were rejected under 35 U.S.C. §112, first paragraph as lacking sufficient written description; claims 21-23 were rejected under 35 U.S.C. §112, second paragraph as indefinite; claims 1-6, 12, 17-20 and 23 were rejected under 35 U.S.C. §102(a) over WO 98/44106 to Waeber ("Waeber"); claim 7 was rejected under 35 U.S.C. §103(a) over Waeber in view of Yang et al., Nature 389:865-70, 1997 ("Yang"); and claim 13 was rejected under 35 U.S.C. §103(a) over Waeber in view of USPN 6,083,713 to Manly et al. ("Manly").

Claims 1, 3, 17, 19 and 21-23 are amended above. The amendments regarding inhibiting c-Jun phosphorylation are supported throughout the application as filed, see for example p. 6-7 and Example 3 at p. 31. Support for the amendments regarding the neurological disease or disorder or apoptosis being mediated by JNK3 can be found throughout the application as filed, for example at pages 1-2, p. 4 lines 16-18, and p. 31 lines 15-19. The additional amendments either delete subject matter or involve changes in transitional phrases suggested by the Examiner. No new matter is added.

The enablement rejection

Claims 1-7, 12-13 and 17-23 were rejected as lacking enablement. This rejection is traversed.

The Office Action stated that the specification discloses the polypeptide comprising SEQ ID NO: 2, the peptide of SEQ ID NO: 3, a method of inhibiting c-Jun phosphorylation by JUNK3 by administering the polypeptide of SEQ ID NO: 2 *in vitro*, as well as a method of generating an antibody, the expression of hJIP1 in the hippocampus and cerebellum, and the expression of hJIP1 in acute hypoxia and under chronic hypoxic stress. The specification was said to lack teaching as to how to make any sequence substantially equivalent to SEQ ID NO: 2, and was said to lack any teaching as to which amino acid can be substituted, deleted, added or mutated, and whether it would have the same function.

Modifications of the polypeptide are taught extensively at p. 19 line 1 to page 20 line 25. Additionally, the regions of the polypeptide responsible for the inhibition of c-Jun phosphorylation are extensively taught in Example 3 and at p. 6 line 21 to page 7 line 7. Applicants also teach how to assay a polypeptide deletion mutant (clone 2.5 is demonstrated, and other deletions are described by results). One of skill following these teachings could make a polypeptide substantially equivalent to SEQ ID NO: 2 by deleting one or more residues taught to be dispensable in the application for inhibiting the phosphorylation of c-Jun by JNK3 without undue experimentation. Applicants need only teach one method of making and using the scope of the invention to meet the test of enablement. *In re Fisher*, 427 F.2d 833, 839, 166 USPQ 18, 24 (CCPA 1970). By teaching how to make deletion mutants falling within the full scope of the claim, Applicants have met the test of enablement. Regions capable of deletion without affecting activity would also be expected to tolerate substitutions and insertions.

The Office Action additionally stated that applicants did not teach a route of delivery that would be expected to cross the blood-brain barrier or to reach the hippocampus or cerebellum. This is not correct. Applicants teach intrathecal administration, as noted in the Office Action. Intrathecal administration involves administration into the cerebrospinal fluid bathing the spinal cord and the brain. *See* Appendix A. Intrathecal administration of the polypeptide human beta-endorphin to the rat has been shown to result in activity of the peptide throughout the rat central nervous system, including changes in the hippocampus. *Id.* Thus Applicants teach a route of administration effective to administer a polypeptide to the brain, including the hippocampus, thereby enabling the invention.

Additionally, the specification was said to provide no showing that hJIP-1 can actually inhibit apoptosis. However, Applicants teach that murine JIP-1 overexpression in PC-12 cells inhibits the NGF withdrawal-induced apoptosis of those cells. *See* p. 2 lines 18-19. Murine JIP-1 displays a high degree of sequence identity with the human homolog, and would be expected to provide the same effect in human cells. Thus there is no legitimate scientific reason to doubt the ability of JIP-1 to inhibit apoptosis.

The Training Materials For Examining Patent Applications With Respect To 35 U.S.C. Section 112, First Paragraph-Enablement Chemical/Biotechnical Applications ("Training Materials") teach that:

There are many factors to be considered when determining whether there is sufficient evidence to support a determination that a disclosure does not satisfy the enablement requirement and whether any necessary experimentation is "undue." These factors include, but are not limited to:

1. the breadth of the claims,
2. the nature of the invention,
3. the state of the prior art,
4. the level of one of ordinary skill,
5. the level of predictability in the art,
6. the amount of direction provided by the inventor,
7. the existence of working examples, and
8. the quantity of experimentation needed to make or use the invention based on the content of the disclosure. *In re Wands,* 858 F.2d 731, 737, 8 USPQ2d 1400, 1404 (Fed. Cir. 1988) (reversing the PTO's determination that claims directed to methods for detection of hepatitis B surface antigens did not satisfy the enablement requirement).

In *Wands*, the court noted that the there was no disagreement as to the facts, but merely a disagreement as to the interpretation of the data and the conclusion to be made from the facts. *In re Wands,* 858 F.2d at 736-40, 8 USPQ2d at 1403-07. The court held that the specification was enabling with respect to the claims at issue and found that "there was considerable direction and guidance" in the specification; there was "a high level of skill in the art at the time the application was filed;" and "all of the methods needed to practice the invention were well known." Id. at 740, 8 USPQ2d at 1406. After considering all the factors related to the enablement issue, the court concluded that "it would not require undue experimentation to obtain antibodies needed to practice the claimed invention." Id., 8 USPQ2d at 1407.

It is improper to conclude that a disclosure is not enabling based on an analysis of only one of the above factors while ignoring one or more of the others. The examiner's analysis must consider all the evidence related to each of these factors, and any conclusion of non-enablement must be based on the evidence as a whole. Id. at 737 & 740, 8 USPQ2d at 1404 & 1407.

Training Materials at III. These factors are analyzed in turn below.

The breadth of the claims. The pending claims encompass methods using completely disclosed polypeptides, and polypeptides at least about 98% identical thereto while retaining relevant kinase inhibitory activity, to treat neurological diseases or disorders or to inhibit apoptosis which are mediated by the kinase activity that the polypeptides inhibit. The breadth of these claims is consistent with the breadth of claims allowed by the PTO.

The nature of the invention. The claimed invention is a biotechnological invention relating to administration of polypeptides to inhibit JNK-mediated neurological diseases or disorders or apoptosis.

The state of the prior art. The state of the prior art was such that one of skill in the art was capable of conducting systematic mutagenesis analysis of every residue of a disclosed sequence in a systemic fashion for over a decade prior to the instant invention without undue experimentation. Numerous reports reflect this. The prior art also taught production of recombinant proteins, methods of performing kinase assays, and intrathecal administration of polypeptide compounds to affect internal compartments of the brain. *See* Appendix A.

The level of one of ordinary skill in the art. The level of one of skill in the art of biotechnology is high, requiring at least a Ph.D in molecular biology, biochemistry or a related discipline, experience in generating mutants of a gene, sequencing, and expression and functional characterization of such resulting mutants, and experience in animal models using the administration of recombinant protein.

The level of predictability in the art. The level of predictability in the art is such that a completely disclosed sequence would be expected to tolerate substitutions, insertions and deletions yielding functional mutants thereof. The level of predictability is such that the teaching of a region of a polypeptide responsible for a given function would allow one of skill to replicate those findings and to reproduce them without undue experimentation.

The Amount of Direction Provided by the Inventor. Applicants have provided considerable disclosure regarding the region of hJIP1 responsible for binding to c-Jun and inhibiting its phosphorylation by JNK3, methods of generating mutants of hJIP1, methods of assaying the resulting mutants for inhibiting activity, methods of administration of polypeptides, mechanisms of action of the polypeptide, and particular diseases and disorders mediated by such mechanisms. Applicants provide working examples of the claimed methods using the compositions of SEQ ID NO: 2 and deletion mutants thereof, many of which are even less than substantially equivalent (less than about 98% identical) to SEQ ID NO: 2, as defined in the application. Working examples of testing bacterially expressed fragments of SEQ ID NO:2 for their ability to bind to c-Jun and inhibit its phosphorylation by JNK3 are provided in

Example 3 at p. 31 and p. 6 line 21 to p. 7 line 7. All these methods were within the skill of the art at the time the invention was made.

The Existence of Working Examples. Applicants provide working examples of using the compositions of SEQ ID NO: 2 and deletion mutants thereof, as defined in the application, to inhibit phosphorylation of c-Jun by JNK3. Working examples of testing bacterially expressed fragments of SEQ ID NO:2 for their ability to bind to c-Jun and inhibit its phosphorylation by JNK3 are provided in Example 3 at p. 31 and p. 6 line 21 to p. 7 line 7. *In vivo* working examples of natural expression of such proteins and of their activity in acute and chronic hypoxic models is also provided.

The Quantity Of Experimentation. As set forth above, Applicants provide detailed teachings regarding the specific region of hJIP1 responsible for inhibition of c-Jun phosphorylation by JNK3. One of skill in the art could make and use a polypeptide substantially identical to SEQ ID NO: 2 with minimal experimentation following the detailed teachings of the regions of that polypeptide which are dispensable for inhibition of c-Jun phosphorylation by JNK3.

The teaching of a method of making and using one embodiment falling within the scope of the claims is sufficient to satisfy enablement. *In re Fisher*, 427 F.2d 833, 839, 166 USPQ 18, 24 (CCPA 1970). "[A] considerable amount of experimentation is permissible, if it is merely routine, or if the specification in question provides a reasonable amount of guidance with respect to the direction in which the experimentation should proceed." *In re Wands*, 858 F.2d at 737, 8 USPQ2d at 1404 (citing *In re Angstadt*, 537 F.2d 489, 502-04, 190 USPQ 214, 218 (CCPA 1976)). Any experimentation used to practice the claimed invention is completely routine to one of skill in the art.

Furthermore, the settled expectations of patent applicants are paramount and are accorded great weight. *Festo Corp. v. Shoketsu Kinzoku Kogyo*, 535 U.S. 722, 152 L.Ed.2d 944 (2002). The PTO has been consistently allowing claims of such scope to the claims presented here. The PTO has consistently found such scope enabled. Applicants request only that their claims be examined in accordance with the settled expectations of applicants in this field and consistently with other applications.

Accordingly, the presented claims are asserted to be fully enabled, and the application teaches one of skill in the art how to make and use the full scope of the invention. It is respectfully submitted that all of the Wands factors are in favor of the enablement of the pending claims. Withdrawal of the enablement rejection is respectfully requested.

The written description rejections under 35 U.S.C. §112, first paragraph

Claims 1-7, 12-13 and 17-23 were rejected under 35 U.S.C. §112, first paragraph as lacking sufficient written description. This rejection is traversed.

The specification was said to lack a written description of treating any neurological disorder with a polypeptide substantially equivalent to SEQ ID NO: 2. The claims have been amended to clarify that the disease, disorder or apoptosis be one that is mediated by JNK3. Support for those amendments can be found at least at pages 1-2, p. 4 lines 16-18, and p. 31 lines 15-19. The support for substantially equivalent polypeptides is set forth above regarding enablement and hereby incorporated. Deletion mutants of SEQ ID NO: 2 having the described limitations are taught in detail in the application. Methods for treating neurological diseases are taught extensively at page 3 line 28 to page 5 lines 10-14.

The Office Action asserts that *Regents of the Univ. Calif. v. Eli Lilly & Co.* and the Written Description Examination Guidelines (Guidelines for Examination of Patent Applications Under the 35 U.S.C. 112, ¶ 1 "Written Description" Requirement, 66 Fed. Reg. 1,099 (Jan. 5, 2001); "Written Description Guidelines") support this rejection.

Neither citation supports the rejection. *Lilly* was an extreme case where the applicants had no structural information on a sequence they attempted to claim through purely functional language. *Lilly* has been effectively limited to its facts by subsequent court decisions, with the CAFC stopping just short of overturning it. See *Moba, B.V. v. Diamond Automation, Inc.*, (Fed. Cir., No. 01-1063, 4/1/03, citing *Enzo*) and *Enzo Biochem v. Gen-Probe Inc.* on rehearing 296 F.3d 1316, 63 USPQ2d 1609 (Fed. Cir. 2002) especially the concurrences and dissents therein (although not precedential).

As strongly emphasized in those cases, the written description requires only that an application reasonably convey to one of skill in the art that the inventor(s) were in possession of the invention at the time of filing.

The Written Description Examination Guidelines (Guidelines for Examination of Patent Applications Under the 35 U.S.C. 112, ¶ 1 "Written Description" Requirement, 66 Fed. Reg. 1,099 (Jan. 5, 2001); "Guidelines") explicitly state:

> An applicant may also show that an invention is complete by disclosure of sufficiently detailed, relevant identifying characteristics which provide evidence that applicant was in possession of the claimed invention, i.e., complete or partial structure, other physical and/or chemical properties, functional characteristics when coupled with a known or disclosed correlation between function and structure, or some combination of such characteristics.

Id. at 1106.

Here the claims recite structural limitations, and fully meet the parameters set forth in the Guidelines. The complete structure of SEQ ID NO: 2 is provided. Furthermore, a deletion mutant (clone 2.5) lacking >10% of the sequence (the first 75 amino acids) was shown to inhibit phosphorylation of c-Jun by JNK3 in a concentration dependent manner. *See* Example 3, page 31. In fact, Applicants have characterized the c-Jun binding domain as extending from about residues 127 to 285. *See* p. 6 lines 22-23. Additionally, Applicants have demonstrated a correlation between the structure of the proteins and the functions described.

The claimed invention is fully described, and one of skill in the art would readily understand that description and appreciate that the inventors were in possession of the invention at the time of filing. The working examples demonstrate this. Applicants are entitled to some scope to their invention, and the scope of the term "substantially equivalent" is described in the application and is consistent with claims allowed by the Office. Withdrawal of the rejection is respectfully requested.

The rejections under 35 U.S.C. §112, second paragraph

Claims 21-23 were rejected under 35 U.S.C. §112, second paragraph as indefinite on for using the terms "has" or "having." The terms have been replaced with "comprises" or

"comprising," respectively, as suggested by the Examiner. Withdrawal of the rejection is respectfully requested.

The rejections under 35 U.S.C. §102(a)

Claims 1-6, 12, 17-20 and 23 were rejected under 35 U.S.C. §102(a) over WO 98/44106 to Waeber ("Waeber"). This rejection is traversed.

For a reference to anticipate a patent claim, all the elements of the claimed invention must be found in that single reference. Waeber fails to teach a polypeptide effective to inhibit c-Jun phosphorylation by JNK3, and therefore fails to teach all the claim elements of the pending claims. Waeber therefore cannot anticipate the claims.

Waeber neither literally nor inherently anticipates the claimed invention. Waeber identified IB1 on the basis of its purported action as a transcriptional activator involved in the control of the GLUT2 and insulin genes by interacting with *cis*-regulatory elements in their promoters. Waeber also does not teach a route of administration effective to treat a neurological disease using IB1. Unlike Applicants, who teach intrathecal administration, Waeber does not teach a route of administration capable of crossing the blood brain barrier. Therefore Waeber is not enabling for teaching a method of treating a neurological disease in any form, much less the invention as claimed.

Waeber cannot inherently anticipate the claimed invention, because one following the teachings of Waeber would not necessarily result in a polypeptide effective to inhibit c-Jun phosphorylation by JNK3 and could not administer an effective amount of such a polypeptide to treat a neurological disease. Inherency requires that the element(s) not expressly taught in the cited reference must necessarily be present, and cannot be established by probabilities or possibilities. MPEP 2112. Waeber describes the use of IB1 agonists and mutants of IB1, including deletion mutants. One following the teachings of Waeber would be directed to use a portion of IB1 that bound to the promoter regions taught in Waeber, and therefore would not necessarily use the portion of hJIP1 responsible for inhibiting phosphorylation of c-Jun by JNK3. Therefore Waeber does not inherently teach this missing claim element.

Additionally, Waeber teaches away from the region of hJIP1 responsible for inhibiting phosphorylation of c-Jun and teaches toward the region of IB1 asserted to bind to specific DNA

sequences in the promoter region. One of skill in the art following the teachings of Waeber would work with the alleged DNA binding regions of the protein, rather than the domain responsible for inhibition of c-Jun phosphorylation by JNK3, which activity Waeber did not even recognize.

By contrast, Applicants have provided extensive experimental results detailing the biochemical activity of hJIP1 as an inhibitor of JNK3 phosphorylation of Jun kinase and as a substrate for JNK3. *See* Example 3, p. 31, and references cited above. Applicants have taught the regions of hJIP1 responsible for inhibiting the phosphorylation of c-Jun by JNK3, have provided extensive teachings in an animal model of neuronal stress induction, including the demonstration of JNK activity and of c-Jun phosphorylation in this animal model. *See* pages 6-8, the Figures and the Examples.

As the cited reference neither expressly nor inherently teaches the claimed invention, is not enabling therefor, and teaches away from , it does not anticipate the claimed invention. Withdrawal of the rejection is respectfully requested.

The rejection under 35 U.S.C. §103(a) over Waeber in view of Yang

Claim 7 is rejected under 35 U.S.C. §103(a) over Waeber in view of Yang et al., Nature 389:865-70, 1997 ("Yang"). This rejection is traversed.

Waeber fails to teach a polypeptide effective to inhibit c-Jun phosphorylation by JNK3. Yang does nothing to cure this critical deficiency. Yang deals simply with knockout mice lacking the JNK3 gene. Disruption of JNK3 was found to cause mice to be resistant to toxicity caused by the glutamate-receptor agonist kainic acid, yielding fewer seizures and less hippocampal neuron apoptosis.

Yang teaches nothing of IB1 or hJIP1, much less their ability to inhibit the phosphorylation of c-Jun by JNK3. Thus at least this element of the claims is completely absent from the cited references.

As the cited references fail to teach all the claim limitations, they have not established a *prima facie* case of obviousness of the claimed invention. Withdrawal of the rejection of claim 7 over Waeber in view of Yang is respectfully requested.

The rejections under 35 U.S.C. §103(a) over Waeber in view of Manly

Claim 13 was rejected under 35 U.S.C. §103(a) over Waeber in view of USPN 6,083,713 to Manly et al. ("Manly"). This rejection is traversed.

Waeber fails to teach a polypeptide effective to inhibit c-Jun phosphorylation by JNK3. Manly does nothing to cure this critical deficiency. Manly is cited for the proposition that liposomes are well know delivery vehicles for hydrophobic drugs and may be used in targeted delivery systems, including to neurons.

Manly thus teaches nothing of IB1 or hJIP1, much less its ability to inhibit the phosphorylation of c-Jun by JNK3. Thus at least this element of the claims is completely absent from the cited references.

As the cited references fail to teach all the claim limitations, they have not established a *prima facie* case of obviousness of the claimed invention. Withdrawal of the rejection of claim 13 over Waeber in view of Manly is respectfully requested.

CONCLUSION

Applicants respectfully request reconsideration of the claims in view of the above amendments and remarks. A notice of allowance is earnestly solicited. If a telephone conference would expedite allowance of this matter, the Examiner is welcome to contact the undersigned at (650) 849-4908.

If an appropriate payment does not accompany or precede this submission, the Commissioner is hereby authorized to charge any required fees, including any petition for extension of time, or to credit any overpayment, to Deposit Account No. 50-2518, billing reference no. 13761-7030 (7002993002).

Respectfully submitted,

By:_____
David W. Maher
Reg. No. 40,077

Bingham McCutchen LLP
Three Embarcadero Center, Suite 1800
San Francisco, California 94111
Telephone: (650) 849-4908
Telefax: (650) 849-4800

APPENDIX A

Intrathecal

<anatomy> Within a sheath, for example, cerebrospinal fluid that is contained within the dura mater. It also refers to drugs administered into the cerebrospinal fluid bathing the spinal cord and brain.

(30 Sep 1997)

Previous: intrastromal, intrasynovial, intratarsal, intratendinous bursa of elbow
Next: intrathecal chemotherapy, intrathecal injection, intrathoracic

Published at the Dept. of Medical Oncology, University of Newcastle upon Tyne

1: Anesthesiology. 1992 Nov;77(5):992-7.

Histologic examination of the rat central nervous system after intrathecal administration of human beta-endorphin.

Hee P, Klinken L, Ballegaard M.

Institute of Neuropathology, University of Copenhagen, Denmark.

The objective of this study was to evaluate histologically the toxicity of human beta-endorphin on the rat central nervous system after intrathecal administration. Animals received a single injection of 5 micrograms (n = 9) or 50 micrograms (n = 10) on each of four consecutive days, while others received 50 micrograms (n = 8) as a single dose. The control groups received either physiologic saline (n = 10) during each of four consecutive days or hac sham operations (n = 4). Tests for nociception (tail-flick latency), motor function, and reflexes (righting reflex, eye-blink reflex, and inclined plane) were performed 5, 15, 30, 60, and 120 min after injection. Both dosages produced a dose-dependent impact on these parameters. In the 50-microgram group, there were no significant differences in analgesia between the first anc the fourth doses injected. The 50-micrograms dose produced catalepsy in some animals. All changes returned to baseline within 24 h. One animal in the 50-micrograms group developed hind limb paralysis after a single injection. Histologic sections from brain, brain stem, and spinal cord were prepared. No changes in histology were found except for that in the paretic animal, which had anoxic changes in the hippocampus and other cortical areas. Human beta-endorphin produced no neurotoxicity. The effect on nociception, reflexes, and motor function confirmed the results of previous studies.

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